

POST PRANDIAL PLASMA GLUCOSE LEVEL LESS THAN THE FASTING LEVEL IN OTHERWISE HEALTHY INDIVIDUALS DURING ROUTINE SCREENING

Biswajit Saha

Dept of Biochemistry, Durgapur Steel Plant Hospital, Durgapur – 713 205, West Bengal, India.

ABSTRACT

During routine screening, some otherwise healthy individuals who showed remarkably lower post prandial (at 2 hour) plasma glucose without any symptom were subjected to extended glucose tolerance test and a few of them to extended post meal tolerance test as well. It was observed that post prandial (at 2 hour) plasma glucose after glucose administration was significantly lower than the fasting level ($p<0.05 - p<0.001$). However, post prandial plasma glucose at 2 hour after their usual meal exhibited a significantly higher level than the fasting and post glucose level ($(p<0.05 - p<0.001)$). Glucose appears to be a stronger agent than the more natural mixed meal in these individuals in causing post prandial lowering of plasma glucose. Hence, these individuals are to be evaluated with their usual meals before considering further investigations. Like upper limit, there is the need to have a consensus lower limit of reference interval of blood glucose level.

KEY WORDS

Plasma glucose, Idiopathic reactive hypoglycemia, Extended glucose tolerance test, Extended meal tolerance test.

INTRODUCTION

Studies have been made on symptomatic cases with possible diagnosis of post absorptive hypoglycemia (1-3). However, the symptoms of hypoglycemia are nonspecific (1,4,5). Unless a post meal hypoglycemia is diagnosed, reactive hypoglycemia due to pancreatic pathology is unlikely (2). In our general hospital, during daily routine laboratory investigations of otherwise normal individuals coming for casual health check up or routine blood glucose testing to rule out diabetes mellitus in the clinical practices, it is found that the post prandial (PP) level of plasma glucose is remarkably lower than that of fasting (F) level in some cases. This creates a confusion since there is a common perception that in blood, PP glucose level should be higher than fasting (F) glucose level. The repeated investigation subsequently yields somewhat similar type of result. When subjected to extended glucose tolerance test (GTT), it was observed that there was a fall in the PP plasma glucose level less than F

around 2 hr followed by increase to reach the F level by 3 – 3½ hr.; but interestingly, if the PP blood glucose level was determined after usual meal the above type of results were not obtained and PP level exhibited always higher than F level. In order to observe the pattern of glucose tolerance in those above individuals, extended GTT and extended meal tolerance test (MTT) were carried out.

MATERIALS AND METHODS

The patients were selected among the otherwise normal individuals who for the first time subjected themselves for blood glucose investigation and exhibited remarkable lowering of PP level of plasma glucose at 2 hr (post glucose) with less than fasting level. Initial evaluation in some cases ($n=15$), the F level and the PP level were 5.3 ± 0.7 mmol/l and 2.7 ± 0.5 mmol/l, with the PP level about $2.6 \pm 0.5\%$ lower than F. extended GTT was carried out with 75 gms glucose or 1.75 g/kg b.w. up to a maximum of 75 gms after usual daily diet (with more than 150 g carbohydrate per day) and physical exercise for at least preceding three days before the test and similarly extended GTT was done with the usual principal meal (conventional Bengali diet comprising rice, pulses, vegetable and fish curry) within a week of extended GTT. The individuals remained seated and did not smoke during the test. Informed consent was obtained from individuals after details of the

Address for Correspondence:

Dr. Biswajit Saha,
Dept of Biochemistry,
Durgapur Steel Plant Hospital,
Durgapur – 713 205, West Bengal, India.
E-mail : dgp_biswajit@sancharnet.in

procedure were explained to them.

A total of 36 cases ($M=24$, $F=12$) were taken for the study. Some individuals were subjected to extended GTT for 2 ½ hrs, some for 3 ½ hrs while some others for 4 hrs.

Plasma glucose was estimated by GOD-POD method (Ranbaxy/Randox) by completely automated clinical chemistry analyzers - Hitachi 704 and Olympus AU 400 after usual daily calibration and ensuring quality performance before starting analysis and the samples were analyzed along with the other routine samples. Qualitative detection of glucose in urine was accomplished by Benedict's test.

The data have been analyzed by the SPSS statistical software package (licensed version of SPSS statistical software from M/S Binary Symetric Ltd, New Delhi, India). The test of significance was done by paired "t" test, unpaired "t" test and Z test depending on the analysis while the correlation, by Pearson correlation coefficient.

RESULTS

The data have been shown by dividing the total cases primarily in three groups - Gr. A ($n=11$), Gr. B, ($n=17$) and Gr. C ($n=8$) with extended GTT for 2 ½ hr, 3 ½ hr and 4 hr respectively. In addition, Gr. D was made by taking all individuals of Gr. A, Gr. B and Gr. C with results up to 2 ½ hr while Gr. E by Gr. B and Gr. C with that up to 3 ½ hrs. Two cases from Gr. B and 5 cases from Gr. C were subsequently subjected to extended MTT as well after their usual mixed meal.

The p values of individual results are against the results of fasting (F) level in each group. A comparison was also made between the results of extended GTT and that of extended

MTT. Glucose in urine was not detected in any sample.

Gr. A showed significant lowering of plasma glucose level at 1 ½ hr than that of F ($p<0.001$). Gr. B, Gr. D and Gr. E showed lowering of plasma glucose level at 2 hr than that of fasting ($p<0.01 - p<0.001$) while Gr. C at 2 ½ hr ($p<0.001$). However, the levels of plasma glucose at 2 hr and 2 ½ hr are significantly lower than that at 1 ½ hr in Gr. A ($p<0.01$ & $p<0.05$). The levels at 2 ½ hrs compared with that of 2 hr in Gr. B, Gr. D and Gr. E while that from 3 hrs compared with 2 ½ hr in Gr. C are not significantly different. In Gr. C, the plasma glucose level at 4 hr is significantly higher than that at 2 ½ hr ($p<0.01$).

There is significant fall of glucose level from 2 ½ hrs onwards after glucose intake than F ($p<0.01 - p<0.02$). Conversely, the levels of plasma glucose after meal remained significantly higher ($p<0.05 - P<0.01$) from 2 hr to 2 ½ hr than F and the results of the corresponding level of plasma glucose between the two groups from 2 hr to 3 ½ are significantly different ($p<0.05 - p<0.001$). No significant correlation of the plasma glucose levels at different time intervals has been observed.

DISCUSSION

Blood glucose level is maintained by a very complex integrated mechanism involving critical interplay of release of hormones and action of enzymes on key metabolic pathways resulting in a smooth transition normally from a high level of glucose influx following meal / glucose intake to a basal level after 2 – 3 hrs or so. The complexity of the coordinated process explains why some degree of unbalance may result in a fall of blood glucose concentration below the usual levels. Excluding alimentary hypoglycemia, renal glycosuria, hereditary fructose intolerance and galactosemia,

Table 1
Results of extended glucose tolerance test

| | F (mmol/l) | ½ hr | 1 hr | 1½ hr | 2 hr | 2½ hr | 3 hr | 3½ hr | 4 hr |
|----------|---------------|---------------|---------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| A | 5.4 ± 0.4 | 8.3 ± 1.9 | 5.9 ± 1.8 | $4.8 \pm 0.7^*$ | $4.0 \pm 0.7^*$ | $4.1 \pm 0.8^*$ | | | |
| B | 5.0 ± 0.3 | 8.3 ± 1.7 | 7.3 ± 2.5 | 5.7 ± 1.7 | $4.2 \pm 1.5^*$ | $4.3 \pm 1.2^*$ | $4.0 \pm 0.7^*$ | $4.3 \pm 0.5^*$ | |
| C | 5.3 ± 0.7 | 8.8 ± 2.0 | 6.4 ± 2.2 | 5.0 ± 1.4 | 4.5 ± 1.4 | $3.6 \pm 0.9^*$ | $3.6 \pm 0.4^*$ | $4.0 \pm 0.4^*$ | $4.7 \pm 0.3^*$ |
| D | 5.2 ± 0.5 | 8.4 ± 1.8 | 6.7 ± 2.3 | 5.3 ± 1.4 | $4.2 \pm 1.3^*$ | $4.0 \pm 1.0^*$ | | | |
| E | 5.1 ± 0.4 | 8.5 ± 1.8 | 7.0 ± 2.4 | 5.4 ± 1.6 | $4.3 \pm 1.4^*$ | $4.0 \pm 1.2^*$ | $3.9 \pm 0.7^*$ | $4.3 \pm 0.5^*$ | |

A = Gr. A ($n=11$) up to 2 ½ hr, B = Gr. B ($n=17$) up to 3 ½ hr, C = Gr. C ($n=8$) up to 4 hr,
D = Gr. D ($n=36$), E = Gr. E ($n=25$); # $p<0.05$, * $p<0.01$, * $p<0.001$

Table 2.
Comparison between extended glucose tolerance test and extended post meal tolerance test

| | F | ½ hr | 1 hr | 1½ hr | 2 hr | 2½ hr | 3 hr | 3½ hr |
|----|-----------|-----------|-----------|-----------|------------|------------|------------|------------|
| PG | 5.2 ± 0.3 | 8.2 ± 2.2 | 7.4 ± 2.2 | 5.0 ± 1.4 | 3.9 ± 1.3 | 3.7 ± 1.1φ | 3.7 ± 0.4♦ | 4.2 ± 0.5♦ |
| PM | 4.9 ± 0.6 | 7.7 ± 1.5 | 6.6 ± 0.9 | 5.4 ± 1.2 | 5.8 ± 1.0# | 5.9 ± 0.8♦ | 5.5 ± 0.6 | 5.0 ± 0.3 |

PG – post glucose, PM – post meal , # p<0.05, φ p<0.02, ♦ p<0.01, values are in mmol/L & n=7.

the possible causes of post prandial reactive hypoglycemia (PRH) include high insulin sensitivity, exaggerated response of insulin and glucagon like peptide 1, defects in counterregulation, very lean and /or anxious individuals, after massive weight reduction, women with lower body overweight etc. (6-16). Although third international symposium on hypoglycemia defined hypoglycemia as post prandial symptoms suggestive of hypoglycemia in everyday life accompanied by a fall 2.5 – 2.8 mM or below (capillary or arterialized venous blood), there are slightly higher levels as per some recent text books (17-19). However, according to Whipple's triad, hypoglycemia can be diagnosed if there are symptoms of hypoglycemia, documentation of a low blood glucose level and relief of symptoms after blood glucose level has been raised (20). Like hypoglycaemia, there are consensus criteria for diagnosing diabetes mellitus, impaired fasting and glucose tolerance including the upper limit of both F and PP levels in normoglycaemia (21). However, the main problem is that there is no well accepted lower limit of reference interval for F and PP blood glucose at 2 hrs of standard oral GTT (OGTT). The lack of information in this regard causes further difficulty in interpretation when the standard reference indicates that it would not be appropriate to consider abnormality only by observing low blood glucose level since some of the normal asymptomatic subjects have plasma glucose levels at about 2.2 – 2.8 mmol/l after glucose administration (20,22-24). Keeping the above in view, it appears to be important to take into account as to what extent the lowering of plasma glucose without any symptom may be considered "normal" in the day to day health care, particularly in areas where sophisticated diagnostic facilities are not available to explain this issue specially to a health-conscious and inquisitive individual. OGTT and GTT are not suitable for the diagnosis of PRH due to false positive and false negative results. Hyperglucosidic breakfast test is preferred to ambulatory glycemic control to diagnose this situation (25). Unless the lower limit of normal PP level after 75 gms OGTT is decided or the GTT with usual meals (different for different populations in India) is considered for routine screening, the lowering of PP level after glucose load than fasting will continue to bother particularly if the lowering is remarkably so.

Various observations regarding hormonal secretion in PRH patients and controls have been made. Insulin, immunoreactive insulin, glucagon and growth hormone response in patients were similar to controls (1,26). Plasma total glucagon like immunoreactivity concentrations were significantly increased in hypoglycemic group while plasma glucagon immunoreactivity levels were suppressed in the hypoglycemic group and control. (26). Significant elevation of plasma epinephrine or human growth hormone though observed late in the course of GTT, plasma norepinephrine, glucagon, cortisol levels did not change during the latter phase of the test (27). Increase of cortisol during the phase of clinical hypoglycaemia had been attributed a specific biological finding that differentiates pathological hypoglycaemia from transitory physiological state (28). Serum insulin during GTT peaked significantly earlier than during OGTT. The early secretion may explain lack of symptomatic hypoglycemia in the patients (3).

Unlike others during the course of this study, none of the patient complained of any problem. Hence, they did not suffer from PRH which occurs exclusively after meals typically within 4 hrs of food ingestion (1,3,23,29,30). Only two patients felt hungry at 3 ½ hr after glucose. Pulse rate was not deliberately measured with a view to eliminating the chance of even slight apprehension. Some individuals discontinued after 2 ½ hrs because they did not want to give more blood. There is no definite pattern of glucose tolerance since significantly lower than fasting level occurred after 1 ½ hr to 2 ½ hr. Significantly higher level at 4 hr perhaps indicates the role of counter regulatory hormones in raising the plasma glucose levels. However, after usual meals, the levels are higher. It might be that the insulin response is relatively brisk with glucose than with meal, a more natural stimulus which allows much slower entry of glucose into the intestine due to complex carbohydrate and other factors in the meal like fiber, fat etc which delay absorption.

The lowering of PP level seems to be an incidental finding in some otherwise healthy individuals coming for casual blood sugar investigation. In this study the lowest PP level after

glucose was 1.9 mmol/l but the individual was asymptomatic. Other cases including this case in whom plasma glucose level had been around or less than the defined hypoglycemic level could be attributed to lowered metabolic set point for stimulation of release of counter regulatory hormones. These cases probably appear to represent non pathological idiopathic disorder in the glucose homeostasis.

In view of the above, it may be concluded that i) in some otherwise normal individuals glucose appears to be a stronger factor than the usual meal in causing remarkably low PP plasma glucose level ii) there is a need to have lower limit of reference interval of PP blood glucose after standard OGTT iii) in day to day medical practices, such cases need to be evaluated with their usual mixed meal before considering further investigation.

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